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APPLICANTS	:	Ronald A. Beyerinck, Heather L. M. Diebele, Dan E. Dobry, Roderick J. Ray, Dana M. Settell, Ken R. Spence
SERIAL NO.	:	10/766,651
FILING DATE	:	January 27, 2004
FOR	:	METHOD FOR MAKING HOMOGENEOUS SPRAY-DRIED SOLID AMORPHOUS DRUG DISPERSIONS UTILIZING MODIFIED SPRAY-DRYING APPARATUS

Commissioner for Patents
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Respectfully submitted,

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Filing Date	January 27, 2004
First Named Inventor	Ronald A. Beyerinck
Group Art Unit	1615
Examiner Name	Thurman K. Page
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Examiner Initials*	Cite No. [1]	Include name of the author (in CAPITAL LETTERS), title of the article, (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
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The Process of Spray Drying and Spray Congealing

by Michael J. Killeen

This article discusses two types of sprayed particle production, spray drying and spray congealing. It provides a working knowledge of the actions and interactions involved in these processes.

Introduction

The production of particles from the process of spraying has gained much attention in recent years. These efforts have resulted in applied spray technology being used for the production of particles ranging from pharmaceutical granulations to microencapsulated flavors. The two main categories of spray particle productions are spray drying and spray congealing. Spray congealing is also, but less commonly, known as spray chilling. Both processes rely on formation of a droplet normally containing a suspended material. This material will be coated by a substance, either melted or dissolved in the droplets' media. The action in spray drying is primarily that of evaporation, while in spray congealing it is that of a phase change from a liquid to a solid. One way of looking at spray drying and congealing is that both processes are similar, with the exception of energy flow. In the case of spray drying, energy is applied to the droplet, forcing evaporation of the media with both energy and mass transfer through the droplet. While in spray congealing, energy only is removed from the droplet, forcing the melted media to solidify. The basic principles and equipment used to develop a production process are similar in both cases.

Spray Drying

The production of powdered particles by means of spray drying offers many advantages. Such particles can be manufactured with a fixed configuration, composition, and size. This can avoid uniformity problems, while making the most of selected raw material properties. Examples of this approach are (1) pharmaceutical tablet granulation, where a binder forms a shell around the active, enhancing compressibility and (2) rapid drying which results in free-flowing powders on a continuous basis. Coffee, laundry detergent, milk, and excipients are all excellent examples of spray drying technology. Liquids may also be microencapsulated in a shell of desired material by spray drying emulsions. Today, the primary use of spray drying is still that of drying a powder in a liquid. This application is most frequently used in a continuous mode.

The spray drying process consists of the following steps: (1) Formation of a slurry to be sprayed; this slurry may be a simple concentrated solution or a dispersion of an insoluble material in a solution. (2) The liquid is then atomized into droplets; this action is critical as the droplet size will dictate the equipment size as well as the final product size. (3) The droplet is exposed to a heated gas flow, normally air; this air supplies the energy required to vaporize the solvent. (4) The dry free-flowing powder or encapsulated liquid or solid is collected. Figure 1 shows the unit operation involved in a common spraying process.

Particles produced from the above method are usually spherically shaped with a tight-size distribution and content uniformity. This can be seen in Photo 1 of spray dried lactose.

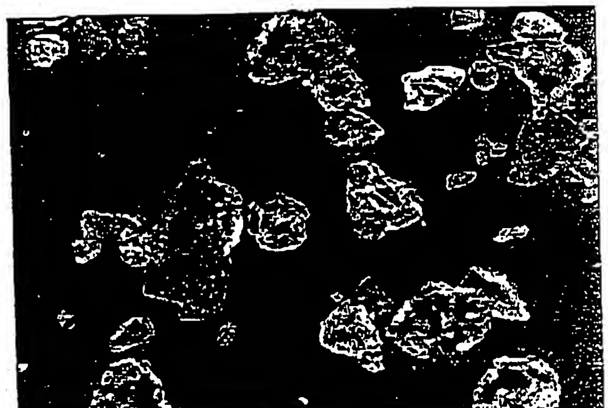

Photo 1. Spray dried lactose.

Particle size can cover a range from 5 µm to 1 mm. More commonly, it averages between 75 µm and 350 µm. However, other properties like porosity, loose and tapped densities, moisture, and friability are influenced by the dryer's design and operations. By combining various spray techniques and drying parameters, a wide range of physical properties are possible for a given substance. This permits the fine tuning of particles for specific needs, often only by changing processing conditions. Photo 2 of maltodextrin is one such example. The particle's bulk density was lowered by increasing the amount of hollow spheres produced by the process.

Regrettably, the name "spray-drying" does not truly convey the large number of ways this truly flexible process can be used.

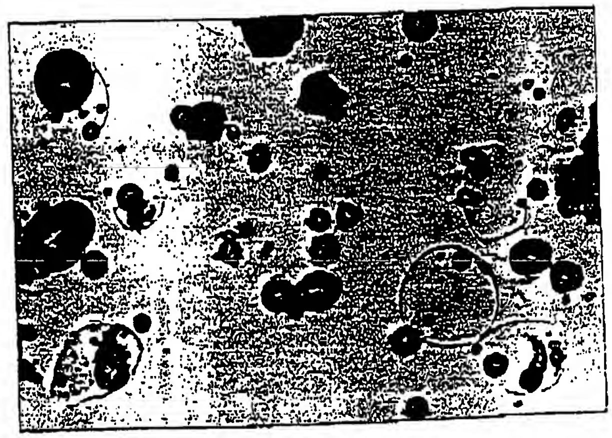

Photo 2. Maltodextrin.

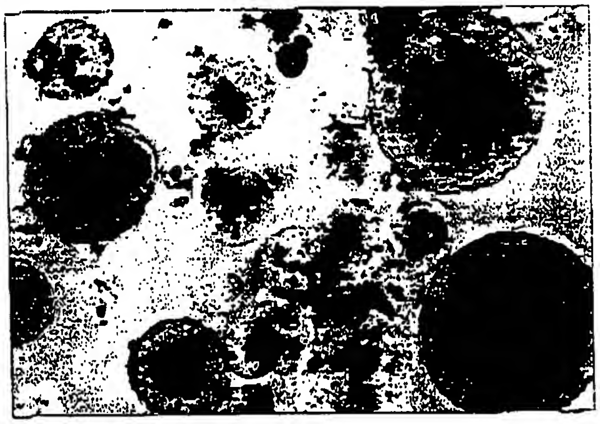

Photo 3. Particles of encapsulated sweetener.

Spray Congealing

In a general sense, spray congealing is quite similar to spray drying. The main differences are the operations that require energy inputs. In spray drying, heated air forces the evaporation of the solvent, while in spray congealing the product is melted by heating. Then droplets are formed and come in contact with chilled air, causing the drop to solidify. This process has been useful in taste masking, forming sustained-release matrices, and improving stability. These benefits are combined with vitamins, such as thiamine mononitrate, riboflavine, and pyridoxine hydrochloride, all to produce chewable children's tablets. A number of artificial sweeteners have been spray congealed to protect them from product's moisture while also delaying sweetness release. As with spray drying, spray congealing lends itself nicely to continuous operation.

The spray congealing process consists of the following steps: (1) Formation of a slurry to be sprayed; this requires melting of the matrix media and dispersion of the material to be encapsulated. In some cases this material may actually be soluble in the media. Both situations are acceptable, with the material being dispersed the more common. (2) The melt is then atomized forming droplets; this action is critical in that it not only specifies the equipment dimensions but also the final droplet configurations. Problems can be caused by the droplet being incorrectly formed as it solidifies. (3) The droplet is exposed to a cooled air flow; this air provides the heat sink necessary for a change in phase to form particles. Many materials cannot be salvaged after this step, so care must be taken to form the correct droplet size and shape. (4) The cooled free-flowing powder is collected; Photo 3 shows particles of encapsulated sweetener, using the above described process, while Figure 2 shows the unit operations in a congealing process.

As with spray drying, spray congealing usually yields particles of similar size and shape. However, properties such as density, moisture, and friability are most often independent of the process. This due to no mass transfer, affecting the particle's properties. The application of a simple phase change with that of spray technology has opened a new avenue for product development.

Equipment

It is always satisfying to have the opportunity to design a new product process with the ideal equipment in mind. Unfortunately, this is most often not the case, and new products must be able to fit existing equipment. A thorough understanding of the nature of various equipment types and the parameters that affect them is important. It can lead to maximum utilization of existing equipment and faster optimizing of new units.

Atomizers

There are four types of atomization devices: air, airless, disk (or rotary) spray, and ultrasonic. The type of spray method used is the major factor in dictating the design of the drier itself. Airless and air spray dryers tend to be tall and narrow, while disk dryers are short and wide. The use of ultrasonic devices to atomize is a new technology, only recently applied to spray drying.

Air atomization or fluid nozzles, as they are also known, can produce the smallest particles of any spray device. They

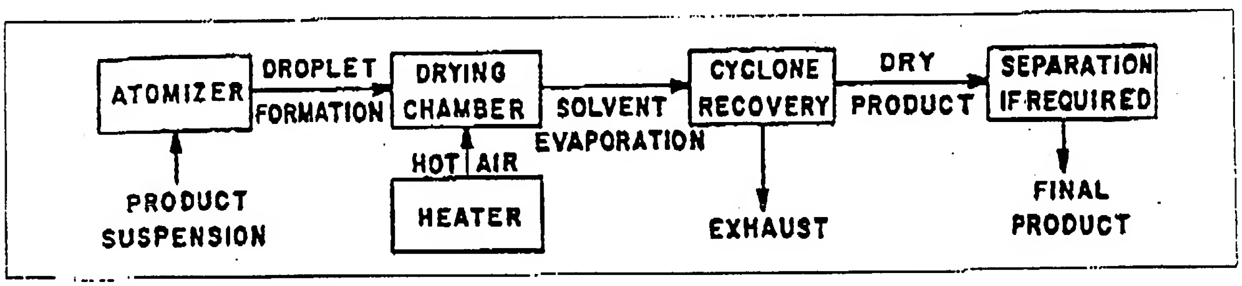

Figure 1. Spray drying unit operations.

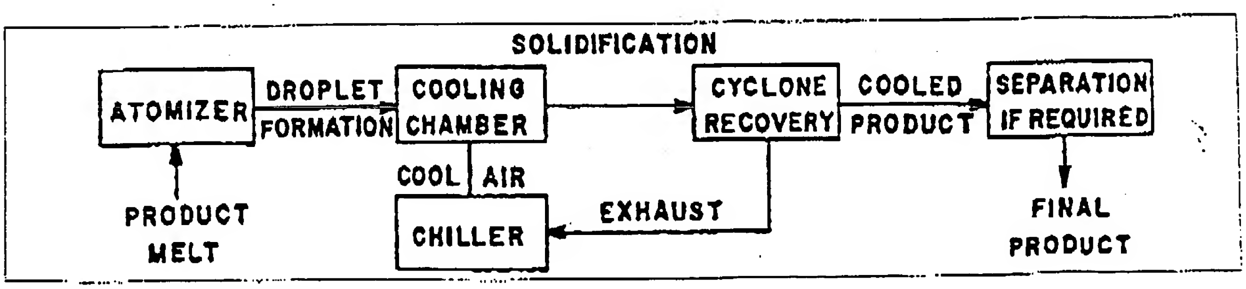

Figure 2. Spray congealing unit operations.

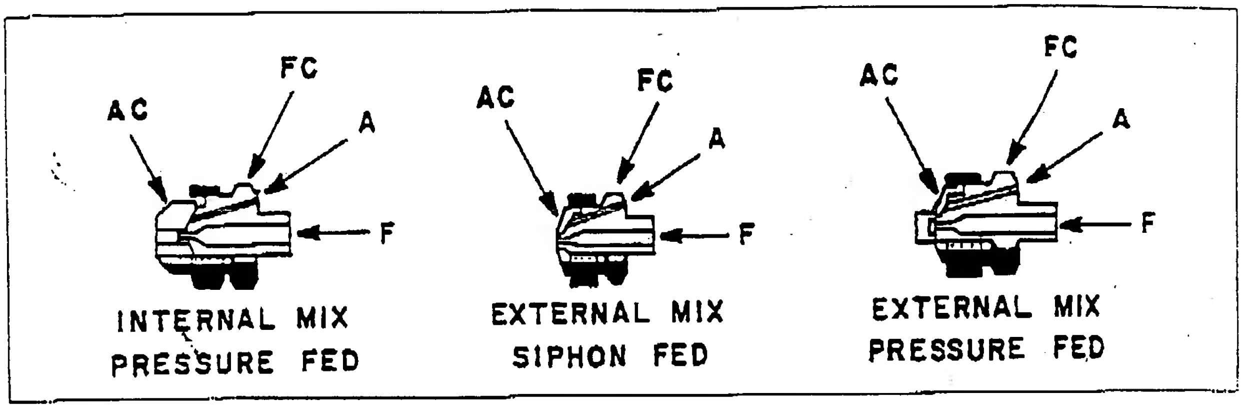

Figure 3. Air atomizing nozzles. (F - fluid, A - air, FC - fluid cap, AC - air cap.)

can also produce the smallest particles at a given pressure and capacity. However, they are most influenced by parameters such as viscosity and pressure differences. Air atomization is used when the desired particle size is below 100 µm. This type of droplet formation allows for the most control, as orifice opening, nozzle pressure, and liquid flow rate can be varied to produce a given particle size. When spray congealing, the atomization air must be heated so as not to cause too rapid solidification. The proper atomization air temperature allows the droplet to form before it congeals. Changes above this temperature point do not affect particle size. However, it may affect the particle's quality due to particle impact, as soft droplets can cause agglomeration.

Figure 3 illustrates the basic design of an air atomizing nozzle. There are two types of air atomizing nozzle designs: internal and external mix. Internal mix nozzles combine the liquid and gas before they exit the nozzle orifice. This type of design is less prone to clogging and is excellent for spray congealing as the first mix can be accomplished while maintaining the product's temperature. As the name implies external mix nozzles combine the gas and fluid flows after they have exited the nozzles' orifices.

Atomization can be varied by changing the gas pressure without affecting the liquid flow rate. There are also two means by which a liquid can be delivered to the nozzle: pressure and siphon or gravity feed. Most spray drying operations use the pressure feed type, as these are less affected by changes in viscosity than are the siphon nozzles.

Air spray nozzles in general, wear less than airless or disk units, which makes them a good choice for abrasive products. High viscosity products are best atomized using external mix nozzles as they have the lowest wear characteristics of any air

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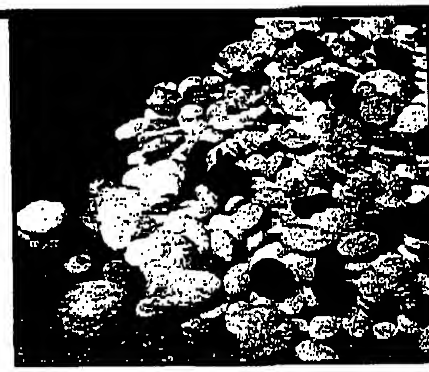

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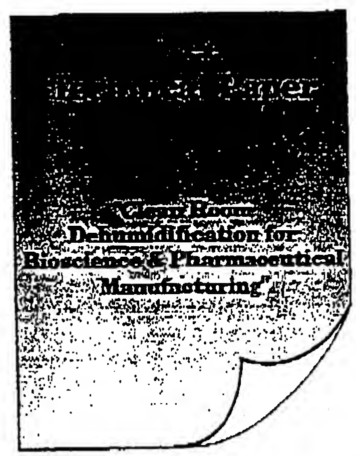

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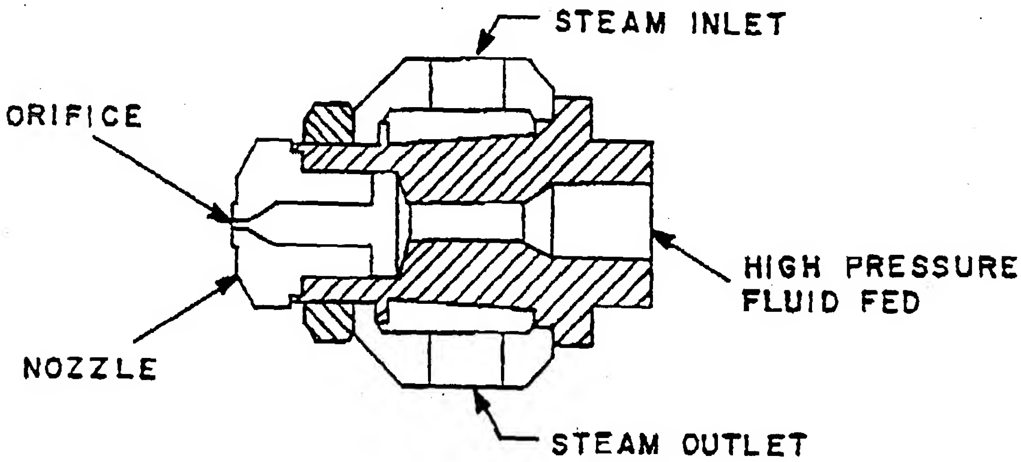

Figure 4. Steam jacketed airless nozzle.

nozzle.

Production rates are controlled by the size of the orifice, liquid feed pressure, and product properties of viscosity and specific gravity. In order to reduce the particle size with air spray, use a smaller orifice opening, a higher atomization pressure, or a wider spray angle. The opposite will produce a coarser product.

Process parameter changes can be used in combination in order to obtain a wide range of effects. Air spraying has the most inherent drying capacity of all the atomization types. This makes it an ideal choice for heat-sensitive products. Its drying characteristics also permit the chamber to be the smallest size possible.

Airless atomization is generally used where the desired final particle size is larger than normally obtained from air atomization or rotary device. Particle sizes are usually above 100 µ. Airless spray does not reflect small changes in product-fed properties in the particles they produce. Hydraulic atomizing, as it is also known, is well suited to feeds having low solid contents. Control of particle size is related directly to orifice opening and feed pressure. High capacities are possible; however, the drying towers tend to be larger than with other types of atomization devices.

These devices are also acceptable for spray congealing. However, keeping the high pressure pumps heated without damage can be difficult. Figure 4 illustrates the basic design of an airless nozzle which has a steam jacket useful for a congealing process. Many designs are available in materials, such as carbide, which will resist wear. This type of atomization does offer the advantage of producing little dust. Airless nozzles yield particles with a tight size range. This can be important in many cases.

Disk (or rotary) atomization involves placement of a liquid on a high-speed rotating plate. As the feed contacts the plate rotating at high speed, it is broken into fine particles by centrifugal force. This design, Figure 5, results in a spray pattern that is wide and short. Hence, this allows the drier to require less head room and greater girth. This type of atomizer can be used with a wide variety of viscosities. Everything from solutions to pastes are processable.

Although multi-nozzles are more common with the other designs, feed rates of up to 200 tons/hour with disk have been noted. Rotary designs are well suited to products which are corrosive, abrasive, and requiring a fine to coarse particle size. These devices are ideal for heat-sensitive products and those that require sanitary construction. Their output particle size is controlled by the speed of the disk and the feed rate. Disk atomizers do not have an inherent drying capacity like the air spray nozzles. However, over the years they have gained widespread acceptance in the pharmaceutical industry, because of their ability to control liquid feeds with less than 20 percent solids.

Disk atomizers are popular for portable pilot laboratory units, as they require a minimum of overhead space.

Recently, ultrasonic energy has been used in place of pressure to form droplets. It works by placing a liquid on a rapidly vibrating surface, at ultrasonic frequencies. When a sufficient amplitude is used the liquid will spread, become unstable, and collapse. This results in the formation of very fine droplets. These devices are excellent for droplets below 50 µm, low flow rates, and low particle velocities. They can be heated and appear well suited to the congealing processes. One can expect to see their use grow over the next few years.

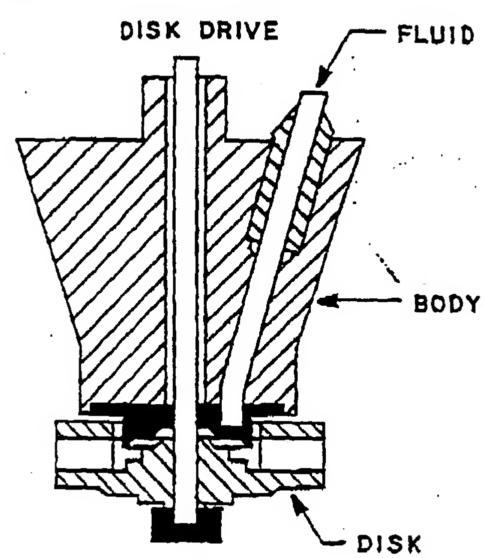

Figure 5. Disk atomizer (rotary).

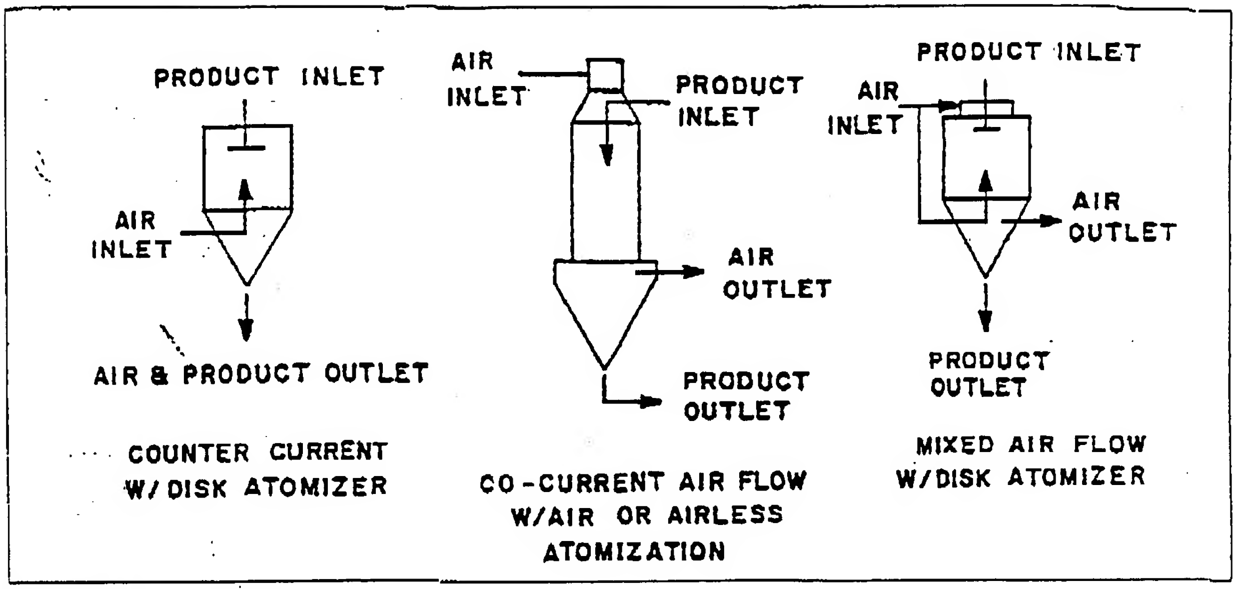

Figure 6. Dryer air flow patterns.

Dryers

Basic size and configuration of a spray dryer are dictated by the atomization device chosen. Disk atomizers primarily require dryers that are wide. This makes them an excellent choice when overhead room is a problem. Disk spray dryers are popular for portable units because their short, wide designs facilitate moving. Air and airless atomizing requires drying chambers that are taller than comparable disk units. These units are favored in operations when multi nozzles are used for high output.

Within the design of the drying chamber, three types of air flow are possible, along with single- or multi-product discharge. Different discharge arrangements can be used to accomplish particle size classification. This feature, when used, can eliminate subsequent unit operation for separation. There are a number of product and drying air input points in

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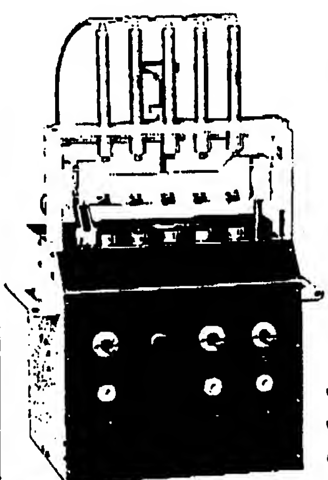

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"...the spray angle can be increased by using a greater atomization or lowering the sprayed media's surface tension."

system's efficiency.

6. Heat capacity is the amount of heat needed to raise a product's temperature 1°C. Latent heat refers to the energy required for evaporation. If it is possible to select a media with a low heat capacity and latent heat, it is advantageous to do so. In the case of spray drying, less energy will be required to raise the droplet's temperature and cause evaporation of the solvent. In the case of spray congealing, less energy will have to be removed from the system in order to cause a phase change. This is known as the latent heat of crystallization.

7. Volatility of a solvent or media is a measure of how readily it evaporates. Needless to say, a high volatility is desirable in any drying process. Unfortunately, available choices are limited today. Organic solvents often require sophisticated safety and environmental equipment in order to meet local effluent regulations. In many cases, these restrict the solvent choice to that of water.

Process Parameters

Impingement is a term for the impact of sprayed droplets onto the dryer side walls. When this condition exists it can greatly affect the system's overall performance. Impingement can be reduced by decreasing the spray angle. Each dryer is limited to a maximum angle of spray by its design. Any change to a product's viscosity or surface tension can affect the spray angle under a given set of atomization conditions. Care should be taken when changing formula so as not to incur a higher rate of impingement. Although tables exist for theoretical coverage of various spray nozzles, they are based on water and do not hold true over long distances. It is best to establish one's own setting, based on data from testing one's own equipment and products.

If needed, the spray angle can be increased by using a greater atomization air pressure or lowering the sprayed media's surface tension. The angle can be reduced by increasing the media viscosity or lowering the atomization. Large changes should be made by using a different nozzle. When using multi-nozzle set-ups, the design should have no spray overlap while utilizing the minimum amount of space possible.

Capacities of production equipment are always an important consideration. In spray drying or congealing, the ability of a system to remove a solvent or cool a material (before discharging it) dictates its maximum capacity. Utilization of high inlet temperatures with high solids usually offers good economics. When processing heat-sensitive materials, multistage and energy recovery units can be effective in increasing efficiency.

Changes in air flow and nozzles are the most common sources of problems, which may occur as the equipment wears over time. The conditions of a dust collector or a fan can often alter the air volume, without external warning signs. These changes can greatly affect the product's quality, which means that their performance should be monitored closely. Nozzle wear is characterized by increased output and changes in spray angle. This will change the droplet size distribution. Periodic inspection of system parts is mandatory in order to maintain uniformity. Most nozzles are produced in a variety of materials with different resistance to abrasion. Most pharmaceutical applications use stainless steel inserts. However, carbide nozzles are often available and offer 40 times the resistance to wear than that of stainless steel.

Process Summary

The impact of the process when spray drying or congealing a product is large. Changes to the processing of a formula can result in a final product having quite different physical characteristics. This leads to product changes due to processing alone. However, it also means tight control limits must be maintained to ensure product consistency and quality.

The use of multistage processes, new spray techniques, and temperature gradient systems hold promise for future pharmaceutical application. Meanwhile, classic equipment designs are gaining popularity in the United States as a means for preparing pharmaceutical products of various types. Their versatility, output capacity, continuous operation, and controllability are desirable features. This type of processing is no longer the sole domain of the bulk chemicals manufacturer.

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